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A Case-Control Study of Dietary Phytoestrogens and Testicular Cancer Risk

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Abstract: *A few dietary studies have found elevated testicular cancer risks for higher red meat, fat, and milk intakes and lower intakes of fruits, vegetables, and fiber. Because hormonal modulation by dietary intake of plant estrogens could affect risk of testicular cancer, we chose to explore the possible relationship between dietary phytoestrogens and testicular cancer. We conducted a hospital-based case-control study of 159 testicular cancer cases diagnosed between 1990 and 1996 and 136 adult friend-matched controls at the University of Texas M. D. Anderson Cancer Center. Amounts of phytoestrogenic compounds in foods were added to the National Cancer Institute's DietSys program and then grouped into prelignans, lignans, flavonoids, isoflavonoids, phytosterols, and coumestrol for statistical analysis, expressed per 1,000 kcal. The results of multivariate logistic regression analysis showed, after adjustment for age, education, income, ethnicity, cryptorchidism, body mass index, baldness unrelated to therapy, severe acne in adolescence, early puberty, daily fiber and fat intake, and total daily calories, no discernable monotonic increased or decreased risk estimates across quartiles of phytoestrogen intake. A U-shaped pattern was observed for lignans and coumestrol. Further evaluation of this pattern by cubic spline parameterization did fit the data, but the data were also consistent with no effect. This hypothesis-generating study does not support the premise that dietary phytoestrogens increase or decrease testicular cancer risk in young men.*

Introduction

Testicular cancer accounts for ~1% of malignant neoplasms in men but is the most common tumor in young adult men aged 20–34 yr in the United States (1,2). Few risk factors, other than cryptorchidism, have consistently been associated with testicular cancer, but an effect of pre- and postnatal endocrine factors likely plays a role (3–19) and could include dietary estrogenic plant compounds (phytoestrogens). A few studies have found increased testicular cancer risk among men whose diets were high in fat, red meats, and milk or low in fiber, fruits, and vegetables (20–22), suggesting that these diets might also be low in phytoestrogens. The fact that dietary factors have been associated with testicular cancer risk supports further investigation of the constituents in diet that may influence risk, particularly phytoestrogen intake, because these estrogenic plant compounds are known to modulate hormone levels in the body (23–28).

Phytoestrogens are naturally occurring compounds found in many plant foods. Technically, they are defined as plant substances or plant precursor derivatives that are structurally or functionally similar to estradiol and consist of a number of subclasses, including isoflavones, prelignans, lignans, coumestrol, flavonoids, and phytosterols. Phytoestrogens have recently become of interest in cancer prevention because of the broad range of anticarcinogenic properties exhibited by these compounds, including antioxidant, antimutagenic, and antiproliferative capabilities (29). Furthermore, recent biochemical studies have shown that phytoestrogens modulate human sex hormone-binding globulin, aromatase, and β-hydroxysteroid dehydrogenase, which are critical in steroid metabolism and production (30–33).

For these reasons, we undertook a hypothesis-generating analysis to explore the relationship of dietary phytoestrogens and risk of testicular cancer. We conducted a hospital-based case-control study at the University of Texas M. D. Anderson Cancer Center. Specifically, we examined whether testicular cancer risk increased, decreased, or showed no relationship as dietary phytoestrogen intake increased. Because age of onset, pathological features, and clinical treatment are different depending on tumor type, we also assessed whether risk estimates for phytoestrogen intake varied by testicular cancer histopathology.

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Methods

We identified men with testicular cancer who registered at the M. D. Anderson Cancer Center between January 1990 and October 1996 through the M. D. Anderson Tumor Registry and the M. D. Anderson Genitourinary Oncology Clinic. Controls were adult male friends of the cases, matched by ethnicity and age within 5 yr. Potential cases and controls were defined as men who were alive during the data-collection phase of the investigation, were between the ages of 18 and 55 yr at the time of case diagnosis, and who lived in Texas, Louisiana, Arkansas, or Oklahoma. Details of the case and control selection, inclusion criteria rationale, and participation rates have been published previously (22). All men diagnosed with testicular cancer were eligible for inclusion, regardless of their ethnicity, tumor stage, and histology. Pathology reports were reviewed for all cases. We grouped teratoma, embryonal carcinoma, and choriocarcinoma as nonseminomas, pure seminomas were grouped as seminomas, and pathology reports with seminomatous and nonseminomatous elements were grouped as mixed germ cell tumors. This research was approved by the University of Texas M. D. Anderson Internal Review Board and the University of Texas-Houston School of Public Health Committee for the Protection of Human Subjects.

Cases and controls completed self-administered questionnaires eliciting information on demographics; lifestyle habits; medical history, including history of cryptorchidism, family history of cancer, puberty onset (based on the age the man reported noticing pubic hair), severe adolescent acne (such that they consulted a physician for it), and balding (unrelated to case cancer therapy); body size and shape; and diet. To assess diet, we used a modified and revised version of the National Cancer Institute's Health Habits and History Questionnaire (HHHQ), which contained 152 foods and beverages (34,35) and has been validated in a range of populations (36,37). The time period assessed by the questionnaire was the year before cancer diagnosis for cases and the previous year for controls. From this information, we calculated food consumption and nutrient intake by using DietSys (version 4.0), the nutrient analysis program developed for the National Cancer Institute's HHHQ (38). The food-frequency questionnaire was modified to include foods that have been previously reported to be significant sources of phytoestrogens. Also, the database was expanded to include phytoestrogen values for foods assessed by the questionnaire. Detailed methodology of the database construction and application to assess prostate cancer risk have been published previously (39,40).

Because there were multiple cases who would be excluded in the analysis of matched data because they did not have a friend control, we evaluated the effect of dissolving the match on our crude and adjusted results. To do so, we compared the unconditional and conditional logistic regression point estimates for all cases and controls, regardless of matching. Because the point estimates in both analyses were essentially the same (data not shown) and to avoid the loss of information, we presented the results with the matching dissolved.

To adjust for total energy intake, all dietary factors were analyzed per 1,000 kcal total energy intake, and total energy intake was included in all models according to the nutrient density adjustment method described by Willett (41). Before analysis of phytoestrogens, a basic model was established, including demographic variables (ethnicity, age, education, and income), known or suspected testicular cancer risk, or beneficial factors (self-reported history of cryptorchidism and early onset of puberty, i.e., pubic hair noticed before age 13), history of severe adolescent acne (severe enough that a physician was seen for the acne), hair loss or balding not due to cancer therapy, body mass index, and important dietary variables (total energy intake, total fat intake, and dietary fiber intake). Body mass index (calculated by dividing weight in kg by height in m^2) and all dietary factors were categorized into quartiles on the basis of distribution among controls. The units and categories of all variables are shown in Table 1. Other variables analyzed that did not improve the base model fit were daily marijuana smoking and milk and meat consumption. We chose this approach because we wished to assess the effect of phytoestrogens in the presence of significant variables in our data.

All phytoestrogens were collapsed into six groups: prelignans, lignans, flavonoids, isoflavonoids, phytosterols, and coumestrol. The original compounds comprising these groupings were prelignans (or lignan precursors of secoisolariciresinol and matairesinol), lignans (enterodiol and enterolactone), flavonoids (quercetin, kaempferol, luteolin, apigenin, and myricetin), isoflavonoids (genistein, daidzein, formononetin, and biochanin A), phytosterols (β-sitosterol, campesterol, and stigmasterol), and coumestrol. Odds ratios for categories of phytoestrogen groups were calculated in a univariate (with addition of 1 phytoestrogen group at a time to the basic model) and in a multivariate way (with addition of all phytoestrogen groups to the basic model).

Linear trend of the log odds ratios was evaluated on the basis of the significance of the slope estimate of the respective continuous variable. All significance tests were two-sided, and the significance level was 0.05. Because this was a hypothesis-generating study and we wanted to reduce assumptions about the nature of the relationships observed, we attempted to more flexibly model the dose response between phytoestrogens and testicular cancer using a cubic spline within a logistic regression model to parameterize the specific phytoestrogen under study. Splines are smooth piecewise polynomial functions of high flexibility with the segments separated by knots (42). In this analysis, two segments were used separated at the median of the phytoestrogen intake among controls.

Results

In total, 187 cases and 148 controls participated in the study. Twenty-eight cases were excluded because their HHHQs were not completed properly, leaving 159 cases for

analysis. Among controls, 12 were excluded because of improper completion of the HHHQ, leaving 136 healthy controls for analysis.

In Table 1, we present selected demographic characteristics for cases and controls grouped by histopathological type. Eighty-one men were diagnosed with nonseminomas, 46 with pure seminomas, and 32 with mixed germ cell tumors. The ethnic distribution, age, education, and income of men with nonseminoma, seminoma, and mixed germ cell tumors were generally similar to those of controls. The only exception was for seminoma, which has a known older age at diagnosis than nonseminoma. History of cryptorchidism was more common in all histological groups than in the controls. Indicators of hormonal status (severe adolescent acne

Table 1. Selected Demographic, Risk Factor Characteristics, and Phytoestrogen Intake of Controls and Testicular Cancer Cases by Histology[a]

		Case's Tumor Type		
Characteristic	Controls (n = 136)	Nonseminoma (n = 81)	Seminoma (n = 46)	Mixed germ cell (n = 32)
Ethnicity				
Caucasian	119 (87.5)	63 (77.7)	38 (82.6)	28 (87.5)
Mexican-American	13 (9.6)	12 (14.8)	6 (13.0)	4 (12.5)
Other	4 (2.9)	6 (7.4)	2 (4.3)	0 (0.0)
Age in 1996, yr				
≤30	46 (33.8)	41 (50.6)	5 (10.8)	10 (31.2)
31–35	26 (19.1)	23 (28.3)	12 (26.0)	12 (37.5)
36–40	24 (17.6)	8 (9.8)	12 (26.0)	4 (12.5)
>40	40 (29.4)	9 (11.1)	17 (36.9)	6 (18.7)
Education, yr				
≤12	24 (17.6)	24 (29.6)	11 (23.9)	10 (31.2)
13–15	28 (20.6)	23 (28.3)	23 (50.0)	10 (31.2)
≥16	82 (60.3)	31 (38.2)	11 (23.9)	12 (37.5)
Unknown	2 (1.5)	3 (3.7)	1 (2.1)	0 (0.0)
Yearly income, $				
<25,000	18 (13.2)	26 (32.0)	10 (21.7)	8 (25.0)
25,000–44,999	27 (19.8)	24 (29.6)	9 (19.5)	3 (9.3)
45,000–64,999	25 (18.4)	12 (14.8)	7 (15.2)	6 (18.7)
65,000	58 (42.6)	14 (17.2)	17 (36.9)	13 (40.6)
Unknown	8 (5.9)	5 (6.1)	3 (6.5)	2 (6.2)
Self-reported history of cryptorchidism				
Yes	3 (2.2)	11 (13.5)	6 (13.0)	3 (9.3)
No	133 (97.7)	70 (86.4)	40 (86.9)	29 (90.6)
Age reported noticing pubic hair, yr				
<13	40 (29.4)	36 (44.4)	20 (43.3)	14 (43.7)
≥13	76 (55.8)	34 (41.9)	18 (39.1)	16 (50.0)
Unknown	20 (14.7)	11 (13.5)	8 (17.3)	2 (6.2)
History of severe adolescent acne				
Yes	34 (25.0)	10 (12.3)	9 (19.5)	2 (6.2)
No	102 (75.0)	71 (87.6)	37 (80.4)	30 (93.7)
History of self-reported balding				
Yes	67 (49.2)	21 (25.9)	18 (39.1)	14 (43.7)
No	69 (50.7)	60 (74.1)	28 (60.8)	18 (56.2)
Body mass index, kg/cm^2				
<23.6	34 (25.0)	29 (35.8)	8 (17.3)	7 (21.8)
23.6–26.4	33 (24.2)	28 (34.5)	19 (41.3)	10 (31.2)
26.4–28.7	35 (25.7)	12 (14.8)	10 (21.7)	5 (15.6)
≥28.7	34 (25.0)	12 (14.8)	9 (19.5)	10 (31.2)
Total daily calorie intake, kcal				
<1,488	34 (25.0)	4 (4.9)	6 (13.0)	3 (9.3)
1,488–1,940	34 (25.0)	13 (16.0)	5 (10.8)	6 (18.7)
1,941–2,705	34 (25.0)	26 (32.0)	15 (32.6)	9 (28.1)
>2,705	34 (25.0)	38 (46.9)	20 (43.4)	14 (43.7)
Total daily fat intake, g/1,000 kcal				
<31.8	34 (25.0)	10 (12.3)	9 (19.5)	4 (12.5)
31.8–36.1	34 (25.0)	12 (14.8)	5 (10.8)	6 (18.7)
36.2–41.1	34 (25.0)	26 (32.0)	16 (34.7)	12 (37.5)
>41.1	34 (25.0)	33 (40.7)	16 (34.7)	10 (31.2)

(Continued)

Table 1. *(Continued)*

Characteristic	Controls (n = 136)	Case's Tumor Type: Nonseminoma (n = 81)	Seminoma (n = 46)	Mixed germ cell (n = 32)
Total daily dietary fiber intake, g/1,000 kcal				
<5.1	34 (25.0)	37 (45.6)	15 (32.6)	12 (37.5)
5.17–6.3	34 (25.0)	11 (13.5)	12 (26.0)	11 (34.3)
6.4–7.9	34 (25.0)	17 (20.9)	11 (23.9)	4 (12.5)
>7.9	34 (25.0)	8 (9.8)	8 (17.3)	5 (15.6)
Total daily prelignans, μg/1,000 kcal				
<275	34 (25.0)	29 (35.8)	13 (30.4)	9 (28.1)
275–697	34 (25.0)	19 (23.4)	9 (19.5)	6 (18.7)
698–1,416	34 (25.0)	17 (20.9)	6 (13.0)	4 (12.5)
>1,416	34 (25.0)	16 (19.7)	17 (36.9)	13 (40.6)
Total daily lignans, μg/1,000 kcal				
<170	34 (25.0)	42 (51.8)	18 (39.1)	14 (43.7)
171–222	34 (25.0)	11 (13.5)	12 (26.0)	9 (28.1)
223–302	34 (25.0)	17 (20.9)	7 (15.2)	5 (15.6)
>302	34 (25.0)	11 (13.5)	9 (19.5)	4 (12.5)
Total daily flavonoids, mg/1,000 kcal				
<4.0	34 (25.0)	31 (38.2)	14 (30.4)	11 (34.3)
4.0–6.4	34 (25.0)	21 (25.9)	7 (15.2)	6 (18.7)
6.5–9.5	34 (25.0)	13 (16.0)	8 (17.3)	10 (31.2)
>9.5	34 (25.0)	16 (19.7)	16 (34.7)	5 (15.6)
Total daily isoflavonoids, μg/1,000 kcal				
<30.6	34 (25.0)	31 (38.2)	14 (30.4)	11 (34.3)
30.6–105.9	34 (25.0)	20 (24.6)	11 (23.9)	6 (18.7)
106.0–474.0	34 (25.0)	16 (19.7)	9 (19.5)	10 (31.2)
>474.0	34 (25.0)	14 (17.2)	12 (26.0)	5 (15.6)
Total daily phytosterols, mg/1,000 kcal				
<71.8	34 (25.0)	30 (37.0)	14 (30.4)	11 (34.3)
71.8–125.7	34 (25.0)	20 (24.6)	9 (19.5)	3 (9.3)
125.8–237.7	34 (25.0)	13 (16.0)	6 (13.0)	4 (12.5)
>237.7	34 (25.0)	18 (22.2)	17 (36.9)	14 (43.7)
Total daily coumestrol, μg/1,000 kcal				
<19.2	34 (25.0)	21 (25.9)	13 (28.2)	11 (34.3)
19.2–42.9	34 (25.0)	22 (27.1)	13 (28.2)	7 (21.8)
43.0–84.3	34 (25.0)	15 (18.5)	6 (13.0)	6 (18.7)
>84.3	34 (25.0)	23 (28.3)	14 (30.4)	- 8 (25.0)

a: Values in parentheses are percentages.

and balding as reported on the questionnaire) were similar between cases and controls, except a greater proportion of cases uniformly reported less adolescent acne and balding. Body mass index was also similar between cases and controls. Total caloric intake among men with testicular cancer was consistently higher across all histological types than among controls, as was total fat intake, whereas total daily fiber intake was consistently lower in cases. Among the phytoestrogen classes, intake was generally similar in cases and controls, except cases tended to consume less total daily lignans than controls.

We present the ranked food items that contributed to the majority of each phytoestrogen for cases and controls in Table 2. In general, the rank order of foods consumed among cases and controls was very similar, except for genistein, daidzein, and enterodiol. For genistein and daidzein, the cases consumed soy nuts and soy meat substitutes, whereas controls consumed miso soup. For enterodiol, cases tended to eat French fries and controls ate green salad.

Univariate and multivariate logistic regression analyses of dietary phytoestrogen groupings (comparing quartiles of consumption) are presented in Table 3. A U-shaped relationship most consistently describes the univariate point estimates for prelignans, lignans, isoflavonoids, phytosterols, and coumestrol for all histological types combined and when analyzed separately. The multivariable estimates, adjusted for age, education, income, ethnicity, cryptorchidism, early onset of puberty (self-reported as the age at which pubic hair was noticed), history of severe adolescent acne, hair loss or balding not due to cancer therapy, body mass index, total energy intake, total fat intake, and dietary fiber intake, show an attenuation of the U-shaped relationship, but it persists for lignans and coumestrol. For seminoma, the odds ratios tended to decrease as lignan intake increased (P for trend = 0.02), showing a relationship pattern slightly different from that of the other phytoestrogens and testicular cancer histologies.

The spline models for lignans and coumestrol tended to support the U shape of the categorical odds ratios. However,

Table 2. Major Foods Contributing ≥10% to Total Phytoestrogen Intake Among Testicular Cancer Cases and Controls

Phytoestrogen Category	Cases	Controls
Prelignans		
Matairesinol	Black tea (95%)	Black tea (91%)
Secoisolariciresinol	Black tea (78%)	Black tea (75%), cranberry juice (13%)
Coumestrol	Refried beans (99%)	Refried beans (99%)
Phytosterols		
β-Sitosterol	Black tea (87%)	Black tea (81%)
Campesterol	Mayonnaise/salad dressing (29%), margarine (14%), dark bread (10%)	Mayonnaise/salad dressing (24%), dark bread (12%), margarine (11%)
Stigmasterol	Mayonnaise/salad dressing (22%), green salad (19%)	Green salad (20%), mayonnaise/salad dressing (18%)
Flavonoids		
Quercetin	Black tea (37%) Cranberry juice (20%)	Black tea (29%) Cranberry juice (24%), onions (11%), spaghetti with tomato sauce (10%)
Kaempferol	Black tea (84%), broccoli (11%)	Black tea (79%), broccoli (14%)
Luteolin, apigenin	Celery (100%)	Celery (100%), cranberry juice (61%)
Myricetin	Black tea (44%), cranberry juice (52%)	Black tea (34%)
Isoflavonoids		
Genistein	Soy nuts (62%), soy meat substitutes (10%)	Miso soup (34%), dried soy beans (13%), soy nuts (13%), tofu (11%)
Daidzein	Soy nuts (68%)	Miso soup (48%), soy nuts (13%), dried soy beans (12%)
Biochanin A	Snow peas (60%), refried beans (20%), lima beans/blackeyed peas (14%)	Snow peas (75%), refried beans (11%)
Formononetin	Dark bread (93%)	Dark bread (95%)
Lignans[a]		
Enterolactone	Cereal, excluding fiber (13%)	None above (10%)
Enterodiol	French fries (14%), other potatoes (12%), green salad (11%)	Green salad (12%), other potatoes (12%), French fries (12%)

a: Mammalian lignans enterolactone and enterodiol are produced in the colon from prelignan precursors in foods. These food values were obtained from a previous study using in vitro fermentation of different food products (44).

confidence intervals (not shown) are very wide. The estimated spline is significantly different from a constant line for coumestrol ($P = 0.02$) and almost significantly different for lignans ($P = 0.07$), but not for other phytoestrogen groups ($P > 0.17$).

Discussion

There are few published studies on the relationship between diet and testicular cancer risk and no studies on phytoestrogen consumption and risk of testicular cancer. To our knowledge, this is the first exploratory analysis of testicular cancer risk and phytoestrogen intake. The results of the present study do not show a linear trend or dose-response pattern associated with phytoestrogen intake and testicular cancer risk. A U-shaped pattern might best describe the relationship between testicular cancer and lignans and coumestrol, but these patterns are only marginally convincing, as evidenced by the weakly suggestive spline modeling results. Prelignans and phytosterols showed a modestly reduced risk for testicular cancer with moderate intake, but not convincingly so. One explanation for these results is the high level of correlation between these compounds, particularly prelignans and phytosterols (data not shown), and so it might be difficult to differentiate the effects of one from the other. Another explanation would be that the associations are spurious because of the limitations of small sample size and inadequate power. On the other hand, it may be that the relationship between estrogenic agents and testicular cancer risk is not straightforward. In a recent study of prenatal diethylstilbestrol (DES) exposure, counterintuitive results were also reported. Among a cohort of men exposed in utero to DES, risk of testicular cancer was elevated in men exposed to lower, rather than higher, levels of DES (19).

There is limited evidence that diet may modulate testicular cancer risk. Previous epidemiological studies on diet and testicular cancer have found a protective effect for consumption of green vegetables on risk for testicular cancer (43) and increased risk of disease with consumption of milk, red meat, total fat, and heterocyclic amines (20,21). A previously published analysis from this study group observed an increased testicular cancer risk associated with high consumption of fat and meat (22) after adjustment for caloric intake.

There are several limitations in our study. Because testicular cancer is relatively rare, to accrue sufficient case numbers, we included men diagnosed up to 6 yr before the questionnaire was administered. The greatest concern is the potential for bias in dietary recall inherent in case-control studies, although Willett (41) suggests that diet can be adequately recalled for up to 10 yr with acceptable levels of

Table 3. Univariate and Multivariate ORs and 95% CIs and Trend Tests for Phytoestrogen Classes and Risk of Testicular Cancer by Histology[a–c]

	All Testicular Cancer		Nonseminoma		Seminoma		Mixed Germ Cell Tumors	
Amount Eaten per Day[d]	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Prelignans, μg/1,000 kcal								
<275	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
275–697	0.66 (0.30–1.45)	0.93 (0.32–2.74)	0.82 (0.30–2.29)	1.50 (0.35–6.34)	0.58 (0.17–1.99)	0.60 (0.11–3.42)	0.74 (0.17–3.11)	2.29 (0.20–26.43)
698–1,416	0.38 (0.17–0.86)	0.46 (0.09–2.33)	0.40 (0.14–1.12)	1.04 (0.12–9.21)	0.28 (0.08–1.04)	0.08 (0.01–1.23)	0.29 (0.06–1.45)	0.13 (0.00–9.15)
>1,416	1.14 (0.52–2.48)	0.96 (0.11–8.09)	0.63 (0.22–1.78)	1.18 (0.05–26.10)	1.16 (0.37–3.62)	0.16 (0.01–4.81)	3.05 (0.74–12.62)	0.66 (0.01–57.52)
P for trend	0.19	0.27	[>0.50]	0.46	0.11	0.27	0.18	>0.50
Lignans, μg/1,000 kcal								
<170	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
171–222	0.64 (0.29–1.44)	0.74 (0.31–1.76)	0.38 (0.13–1.16)	0.51 (0.15–1.72)	0.82 (0.24–2.79)	1.29 (0.31–5.47)	0.70 (0.18–2.73)	0.58 (0.10–3.42)
223–302	0.53 (0.21–1.37)	0.47 (0.17–1.33)	0.82 (0.25–2.73)	0.99 (0.25–3.88)	0.29 (0.06–1.32)	0.19 (0.03–1.10)	0.28 (0.05–1.51)	0.15 (0.02–1.47)
>302	1.01 (0.34–3.04)	0.73 (0.21–2.56)	0.81 (0.17–3.74)	0.82 (0.14–4.68)	0.91 (0.16–5.09)	0.27 (0.03–2.36)	0.70 (0.09–5.47)	0.24 (0.02–3.32)
P for trend	0.09	0.09	[>0.50]	[>0.50]	0.02	0.03	>0.50	>0.50
Flavonoids, μg/1,000 kcal								
<4.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
4.0–6.4	0.77 (0.34–1.76)	1.49 (0.54–4.06)	0.49 (0.17–1.41)	1.02 (0.27–3.81)	0.69 (0.18–2.70)	1.27 (0.23–7.00)	0.56 (0.11–2.94)	1.63 (0.18–14.34)
6.5–9.5	0.82 (0.36–1.85)	1.55 (0.46–5.24)	0.35 (0.11–1.15)	1.09 (0.18–6.47)	1.08 (0.32–3.71)	1.96 (0.27–14.47)	1.20 (0.29–4.95)	3.26 (0.25–43.39)
>9.5	1.40 (0.62–3.15)	2.00 (0.44–9.02)	0.81 (0.27–2.43)	1.98 (0.22–18.00)	1.77 (0.54–5.78)	5.37 (0.50–57.74)	2.96 (0.65–13.44)	5.52 (0.27–113.80)
P for trend	0.24	0.49	>0.50	>0.50	0.39	>0.50	0.02	0.05
Isoflavonoids, mg/1,000 kcal								
<30.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30.6–105.9	0.68 (0.31–1.49)	0.58 (0.25–1.35)	0.75 (0.26–2.12)	0.63 (0.19–2.09)	0.72 (0.20–2.62)	0.41 (0.09–1.87)	0.40 (0.09–1.77)	0.22 (0.03–1.43)
106.0–474.0	0.76 (0.34–1.68)	0.84 (0.36–2.00)	0.73 (0.25–2.17)	0.92 (0.27–3.12)	0.51 (0.14–1.92)	0.52 (0.11–2.41)	1.55 (0.39–6.14)	1.25 (0.22–7.15)
>474.0	0.64 (0.27–1.53)	0.83 (0.33–2.09)	0.42 (0.13–1.37)	0.51 (0.14–1.89)	0.78 (0.21–2.94)	1.21 (0.26–5.70)	0.64 (0.13–3.27)	0.98 (0.13–7.36)
P for trend	>0.50	>0.50	[0.24]	[0.17]	0.12	0.12	[0.47]	[>0.50]
Phytosterols, μg/1,000 kcal								
<71.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
71.8–125.7	0.52 (0.23–1.21)	0.54 (0.18–1.58)	0.62 (0.20–1.85)	0.47 (0.10–2.15)	0.59 (0.16–2.27)	0.69 (0.11–4.41)	0.14 (0.03–0.79)	0.09 (0.01–0.99)
125.8–237.7	0.35 (0.15–0.80)	0.51 (0.12–2.09)	0.28 (0.09–0.86)	0.26 (0.04–1.80)	0.38 (0.09–1.53)	1.41 (0.12–16.30)	0.18 (0.04–0.89)	0.44 (0.02–12.00)
>237.7	0.83 (0.38–1.83)	0.67 (0.13–3.56)	0.40 (0.14–1.17)	0.27 (0.03–2.67)	0.92 (0.27–3.05)	2.01 (0.12–34.32)	1.04 (0.26–4.13)	0.66 (0.02–24.07)
P for trend	>0.50	>0.50	[>0.50]	>0.50	>0.50	[>0.50]	0.32	[>0.50]
Coumestrol, μg/1,000 kcal								
<19.2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
19.2–42.9	1.06 (0.49–2.29)	1.15 (0.51–2.60)	1.26 (0.45–3.52)	1.20 (0.41–3.55)	1.05 (0.34–3.24)	1.23 (0.33–4.52)	0.62 (0.16–2.42)	0.53 (0.10–2.70)
43.0–84.3	0.64 (0.28–1.50)	0.59 (0.23–1.48)	0.62 (0.19–1.98)	0.65 (0.17–2.42)	0.43 (0.10–1.77)	0.33 (0.06–1.82)	0.73 (0.17–3.18)	0.32 (0.04–2.61)
>84.3	1.45 (0.63–3.35)	1.40 (0.56–3.51)	1.57 (0.50–4.92)	1.45 (0.38–5.49)	1.15 (0.31–4.25)	0.84 (0.19–3.71)	1.85 (0.44–7.79)	1.30 (0.19–9.11)
P for trend	0.08	0.07	0.05	0.06	>0.50	>0.50	0.09	0.32

a: Values are odds ratios (ORs), with 95% confidence intervals (CIs) in parentheses.

b: Univariate ORs are adjusted for variables in the base model including ethnicity, age, education, income, history of cryptorchidism, early onset of puberty, history of severe adolescent acne, balding unrelated to cancer therapy, body mass index, total energy intake, total fat intake, and total dietary fiber intake; in addition to these variables, multivariate ORs were also adjusted for phytoestrogen classes.

c: Linear trend test is *P* value for slope estimate using respective continuous variables; brackets indicate a negative slope estimate.

d: Quartiles were determined by the distribution in the controls.

misclassification. We used adult friends of cases as controls, because we thought population-based controls would not reflect the population from which the cases arose, despite the problem that friends might be too "similar" to cases. We do not believe that "overmatching" occurred, because even though our controls were not too dissimilar from cases, they tended to be slightly older and better educated than cases. However, this implies that the associations between diet and testicular cancer may be spurious because of the inclusion of more highly educated controls. For example, the more educated controls may be more conscious of fat intake and methods to reduce dietary fat consumption. However, any conscious dietary alterations based on news reports of soy product benefits (e.g., reduction of prostate cancer risk) postdated data collection, so little impact on phytoestrogen intake can be envisioned.

In conclusion, a comprehensive hormonal mechanism for testicular cancer has not been clearly established, and it should be remembered that phytoestrogens have been noted for actions that suggest estrogenicity or antiestrogenicity, as well as antioxidant effects. Therefore, the mechanism of action of phytoestrogens in humans and cancer risk remains highly speculative. As steroidogenic organs, the human testes are prime targets for hormonal modulation by exogenous hormones. Although we did not find an effect of dietary phytoestrogen intake on testicular cancer risk because the human diet is the primary means of exposure to exogenous hormonal substances, further research on the impact of exposure to phytoestrogens and other hormonally active agents in the diet on testicular cancer risk is warranted.

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